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No. 06-1249

IN THE
Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI TO
THE VERMONT SUPREME COURT

BRIEF FOR PETITIONER

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QUESTION PRESENTED

Whether the prescription drug labeling judgments imposed on manufacturers by the Food and Drug Administration ("FDA") pursuant to FDA's comprehensive safety and efficacy authority under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, preempt state-law product liability claims premised on the theory that different labeling judgments were necessary to make drugs reasonably safe for use.

PARTIES TO THE PROCEEDING

Petitioner Wyeth was the defendant and appellant in the courts below. Respondent Diana Levine was the plaintiff and appellee in the courts below.

CORPORATE DISCLOSURE STATEMENT

Petitioner Wyeth has no parent corporation, and no publicly held company owns 10% or more of its stock.

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The decision of the Vermont Supreme Court is reported at 944 A.2d 179 (Vt. 2006) (Pet. App. 1a-48a). That court denied Wyeth's motion for reargument in an unreported order (Pet. App. 75a-76a). The trial court's decision denying Wyeth's Motion for Judgment as a Matter of Law (Pet. App. 49a-74a) is unreported.

JURISDICTION

This Court has jurisdiction pursuant to 28 U.S.C. § 1257(a). The Vermont Supreme Court entered its judgment on October 27, 2006 and denied a timely motion for reargument on December 11, 2006. The peti-

tion for writ of certiorari was filed on March 12, 2007 and granted on January 18, 2008.

RELEVANT CONSTITUTIONAL, STATUTORY, AND REGULATORY PROVISIONS

The following constitutional, statutory, and regulatory provisions are set forth in relevant part in the appendix to the petition for writ of certiorari:

- The Supremacy Clause, U.S. Const. art. VI, cl. 2 (Pet. App. 77a);
- Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 352, 355, 393 (Pet. App. 78a-111a);
- Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (Pet. App. 112a);
- 21 C.F.R. § 314.70 (Pet. App. 113a-125a).

PRELIMINARY STATEMENT

The Federal Food, Drug, and Cosmetic Act (FDCA) and its amendments charge the Food and Drug Administration (FDA) to protect and promote the public health by reviewing the safety and efficacy of new prescription drugs before permitting their interstate distribution. FDA review of a New Drug Application requires careful balancing of the benefits offered by the drug against the potential risks that inevitably accompany the use of any prescription medicine. *Cf. Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999, 1004-1005 (2008) (analyzing analogous approval requirements for medical devices). The authority to control the content of all the information in a drug's labeling is central to FDA's ability to strike that balance. The agency's comprehensive authority over drug labeling enables FDA to manage the risks associated with each drug in a manner that reduces the potential for harm, while en-

suring that the most efficacious treatments remain available to patients who need them.

Carrying out precisely this balancing of risks and benefits, FDA determined that Wyeth's drug Phenergan is safe and effective for use in the treatment of nausea, and it approved labeling for that drug that permitted intravenous injection as an acceptable method of administering the drug. FDA reached and adhered to this conclusion with full knowledge that exposure of arterial blood to Phenergan can result in severe injury, including gangrene, and that intravenous injection—including "IV push" injection—can lead to inadvertent arterial exposure if performed incorrectly. FDA did not direct Wyeth to contraindicate—i.e., eliminate as a permissible method of administration—IV push or other forms of IV injection, but instead chose to preserve the added effectiveness of intravenous administration and manage this known risk by requiring Wyeth to include carefully tailored warnings and instructions on the drug's labeling. Indeed, since at least 1967, FDA has repeatedly reviewed Phenergan's labeling with respect to arterial blood exposure and mandated that Wyeth distribute the drug only under the verbatim labeling approved by FDA. Absent any newly discovered evidence concerning the nature or degree of these risks, any modification by Wyeth of the contents of these warnings would violate the FDCA and FDA's implementing regulations.

In this case, a Vermont jury was nevertheless permitted to find Wyeth liable for failing to change Phenergan's labeling to eliminate IV push injection from the approved methods of administration. The Vermont Supreme Court affirmed that verdict even though the labeling already contained numerous warnings about the risks associated with IV injection of Phenergan,

and even though respondent never showed or even contended that Wyeth had any material new information about those risks that FDA had not already taken into account when it approved Phenergan's labeling. Compliance with the state-law labeling requirements underlying that verdict would require Wyeth to modify Phenergan's FDA-approved labeling in violation of the FDCA. Moreover, enforcement of this state-law duty would nullify the *ex ante* expert and statutorily mandated balancing of therapeutic benefits and safety risks that FDA performed in approving Wyeth's Phenergan labeling. It would substitute the *ex post* judgment of lay jurors whose members consider drug safety through the lens of a single patient's injury, rather than from the perspective of the overall public health, with the countervailing benefits of the drug to the entire potential patient population in mind. Indeed, counsel for respondent expressly invited the jury to override FDA's decision, telling them "[t]he FDA doesn't make the decision, you do." JA 212.

The judgment below, concluding that Phenergan's labeling should have contraindicated a method of administration that FDA had permitted, thus conflicts with the federal regulatory regime under the FDCA in two ways. First, Wyeth could not change Phenergan's labeling to comply with Vermont law without violating federal law. Second, the state-law requirement frustrates both Congress's objective of having an expert agency balance a drug's risks and benefits and FDA's implementation of that objective in the case of Phenergan. In light of this clear conflict, and under this Court's settled Supremacy Clause precedent, respondent's claims are preempted, and the judgment below should be reversed.

STATEMENT OF THE CASE

I. STATUTORY AND REGULATORY FRAMEWORK

A. Evolution Of FDA's Statutory Authority

The statutory regime under which FDA regulates prescription drugs reflects a pervasive and particularized federal role in regulating the safety and effectiveness of their labeled uses. Drug labeling has been subject to federal control since the 1906 enactment of the Pure Food and Drugs Act. Pub. L. No. 59-384, 34 Stat. 768 (1906). The 1906 Act authorized the federal government to seize drugs that were adulterated or misbranded and to prosecute their manufacturers. *Id.* §§ 1, 2, 5, 10. "Misbranded" drugs included drugs with labeling that was "false or misleading in any particular." *Id.* § 8. The Act did not require premarketing approval, but even during this limited early stage of federal supervision, Congress showed concern about disparate state-law labeling standards and an intent to bring about uniform national labeling. *See* H.R. Rep. No. 59-2118, at 4 (1906) (expressing concern regarding "the varying requirements as to standards and labels in different States" for food products); 40 Cong. Rec. 1217 (1906) (statement of Sen. Nelson) ("[T]he bill will, whenever there is a conflict between the State law and this law, leave this law controlling and be the means of equalizing and doing justice to all parts of the country, instead of having the difficulties we now encounter in many of the States.").

Reacting to mounting evidence of drug safety problems, Congress enacted the FDCA in 1938. Pub. L. No. 75-717, 52 Stat. 1040 (1938). The FDCA precluded interstate shipment of a new drug unless FDA determined that the drug was "safe for use under the conditions prescribed, recommended, or suggested in the

proposed labeling thereof," *id.* § 505(a), (d), 52 Stat. at 1052, and it required that the labeling of all drugs provide "adequate directions for use" and "adequate warnings" against unsafe uses and methods of administration, *id.* § 502(f); *see also id.* §§ 201(p), 301(a), 502, 505(a), (d), 52 Stat. at 1041-1042, 1050-1052 (codified as amended at 21 U.S.C. §§ 321(p), 331(a), 352, 355(a), (d)). The statute prohibited manufacturers from distributing a new drug until a New Drug Application (NDA) for that drug was effective, and it required "specimens of the labeling proposed to be used for such drug" to be submitted as a central component of that NDA. *See id.* § 505(a), (b), 52 Stat. at 1052 (codified as amended at 21 U.S.C. § 355(a), (b)). Thus, if a manufacturer altered a drug's labeling without submitting the proposed changes to FDA, the drug would no longer be one for which an NDA was effective, and interstate distribution of the drug would be unlawful and subject to criminal and civil penalties. *See id.* §§ 201(p), 301(a), (d), 302(a), 303(a), 304, 307, 505(a), (d)(1), 52 Stat. at 1041-1046, 1052 (1938) (codified as amended at 21 U.S.C. §§ 321(p), 331(a), (d), 332(a), 333(a), 334, 337, 355(a), (d)).

In 1962, Congress enlarged FDA's authority by requiring the agency to determine that a drug is not only safe, but also effective "under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" before approving it for distribution. Drug Amendments of 1962, Pub. L. No. 87-781, § 102(b), (c), 76 Stat. 780, 781 (codified as amended at 21 U.S.C. § 355(b), (d)). Congress also gave FDA post-approval authority to require manufacturers to submit reports "of data relating to clinical experience," including adverse drug events, to enable FDA to determine whether to withdraw approval under 21 U.S.C. § 355(e)

on the ground that a drug is not safe or effective under labeled conditions of use. *Id.* § 103(a), 76 Stat. at 782-783 (codified as amended at 21 U.S.C. § 355(k)(1)).[1]

Since the 1962 amendments, determination of a drug's safety has thus been "inseparable from consideration of the drug's effectiveness." *See* S. Rep. No. 87-1744, at 15 (1962). With respect to any NDA, FDA must weigh the safety risks associated with a new drug against the therapeutic benefits it offers and strike a balance between those often competing considerations by regulating "the conditions prescribed, recommended, or suggested in the proposed labeling." *See* 21 U.S.C. § 355(d); *see also* 21 C.F.R. § 314.50(d)(5)(viii) (requiring NDAs to include a "summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling"); FDA, *Guidance for Industry*, *Development and Use of Risk Minimization Action Plans* 4 (Mar. 2005), *available at* http://www.fda.gov/cder/guidance/6358fnl.pdf (describing FDA's risk-benefit assessment as measuring whether, under labeled conditions of use, "the clinical significance and probability of [a drug's] beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects"). In this way, FDA fulfills its dual mission to "protect the public health" by barring access to unsafe or ineffective drugs, and to "promote the public health"

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[1] With the enactment of the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, tit. IX, 121 Stat. 823, 922-962, FDA has enhanced authority to require post-approval labeling changes where "new safety information" comes to light. *See, e.g.*, *id.* §§ 901(a), 902(a), 121 Stat. at 922-926, 943 (codified at 21 U.S.C. §§ 352(z), 355(o)(1), (4)).

by ensuring prompt access to effective and beneficial medicines. 21 U.S.C. § 393(b).

B. FDA's Regulation Of Drug Labeling

"Drug labeling serves as the standard under which FDA determines whether a product is safe and effective." 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985).[2] As such, FDA regulation of labeling serves as "[t]he centerpiece of risk management." 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). FDA-approved drug labeling "communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." *Id.*

FDA regulates drug labeling both through rules of general applicability promulgated under its broad regulatory authority, *see* 21 U.S.C. § 371(a), and through particularized review of the labeling for each individual drug. Under general FDA regulations, a drug's labeling must include "a summary of the essential scientific information needed for the safe and effective use of the drug." 21 C.F.R. § 201.56(a)(1). Labeling must describe the drug and its clinical pharmacology, its indications and usage, contraindications, warnings, precautions, and instructions on dosage and methods of administration, and those sections must appear in a specified order. *Id.* § 201.56(d)(1), (e)(1). FDA regulations also specifically describe the required content of each of those sections, *id.* §§ 201.57, 201.80, and mandate that

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[2] The term "labeling" means "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m).

the labeling describe "adverse reactions," "other potential safety hazards," "limitations in use imposed by them," and "steps that should be taken if they occur," *id.* §§ 201.57(c)(6), 201.80(e).

To ensure that these requirements are met, FDA reviews the labeling submitted with each NDA and supplemental NDA as part of the approval process. FDA may approve an NDA only if it finds that the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof"; that there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof"; and that the proposed labeling is not "false or misleading in any particular." 21 U.S.C. § 355(d). And FDA may withhold approval until the manufacturer makes any necessary changes to the labeling. 21 C.F.R. § 314.105(b); *see also id.* § 314.110(a). Once FDA approves an NDA, it requires the manufacturer to distribute the drug only under the precise labeling approved in the NDA. *See id.* § 314.105(b) ("[A]pproval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.").[3]

[3] Accordingly, upon approving any NDA, FDA instructs the manufacturer that the drug's final printed labeling must match the labeling that was included in the NDA. *See, e.g.*, Letter from Center for Drug Evaluation and Research, FDA, to Idenix Pharms. Inc. approving NDA 22-011 (Tyzeka) (Oct. 25, 2006), *available at* http://www.fda.gov/cder/foi/appletter/2006/022011s000ltr.pdf ("The final printed labeling (FPL) must be identical to the agreed upon enclosed labeling[.]").

The FDCA permits manufacturers to distribute only those drugs that FDA has certified to be safe and effective *under labeled conditions of use*. 21 U.S.C. § 355(a), (b)(1)(F), (c)(1)(A), (d) (emphasis added). Because the FDCA thus prohibits the distribution of drugs for which no application is effective, and because the FDA-approved labeling is a central component of an effective application, a manufacturer may not change a drug's FDA-approved labeling without obtaining FDA's prior approval of a supplemental NDA. *See* 21 U.S.C. § 355(a), (b)(1)(F), (c)(1)(A), (d); *see also* 21 C.F.R. § 314.70(b)(2)(v)(A), (b)(3). A narrow exception to this rule in the FDA regulations permits a manufacturer who has filed a supplemental NDA to implement a labeling change before FDA has acted on the application if the change is intended "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction," or "[t]o add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." 21 C.F.R. § 314.70(c)(6)(iii)(A), (C).[4]

This regulation—known as the "changes being effected," or "CBE," regulation—codifies a longstanding FDA policy under which the agency exercises its enforcement discretion not to take action against a manufacturer that modifies a drug's FDA-approved labeling to add or strengthen warnings without prior approval if the change reflects newly discovered risk information.

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[4] FDA regulations also permit manufacturers to make minor editorial changes to a drug's labeling and changes to the labeling's description of the drug or how it is supplied without submitting a supplemental NDA, so long as the manufacturer documents the change in its annual report to FDA. *See* 21 C.F.R. § 314.70(d)(1), (2)(ix), (2)(x).

See 30 Fed. Reg. 993, 993-994 (Jan. 30, 1965); 73 Fed. Reg. 2848, 2848-2849 (proposed Jan. 16, 2008); *see also* U.S. Br. 13 (Dec. 21, 2007) (CBE regulation constitutes a "limited exception" to prior approval requirement only for changes addressing "*newly discovered risks* from the use of [a] drug" (quoting 47 Fed. Reg. 46,622, 46,623 (Oct. 19, 1982)) (emphasis added in U.S. Br.)). FDA retains ultimate authority to approve or disapprove of the labeling change and to take enforcement action against the manufacturer for misbranding if the change "makes the labeling false or misleading." 71 Fed. Reg. at 3934; *see also* 21 C.F.R. § 314.70(c)(7). Thus, "the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act." 71 Fed. Reg. at 3934.

II. FACTUAL BACKGROUND

A. FDA's Regulation Of Phenergan's Labeling

This case involves a prescription drug called Phenergan® Injection, or simply "Phenergan," which treats nausea and other ailments.[5] FDA approved Phenergan in 1955. JA 266-267. Since then, with Wyeth's cooperation, FDA has engaged in extended review and regulation of Phenergan's uses and risks and the information in its labeling. Phenergan has been approved as safe and effective when administered by deep intramuscular ("IM") or intravenous ("IV") injection. *See, e.g.*, JA 390. As Phenergan's labeling indicates, IV administration produces clinical effects four times faster than IM administration and is therefore beneficial for patients in need of rapid treatment. *See* JA 390; *see also* JA 40-41,

[5] Phenergan is Wyeth's brand name for promethazine hydrochloride, a drug sold by several different drug manufacturers.

60-61; *infra* nn. 10, 11. In one method of IV administration, known as "IV push," the drug is injected (or "pushed") by a syringe that is inserted directly into a patient's vein or into the flexible tubing of an infusion set leading to a needle already inserted into a patient's vein. IV administration can also occur through an "IV drip," whereby the drug is introduced into an infusion system consisting of a hanging IV bag of saline solution that drips down a flexible tube from the bag to a needle or catheter inserted into a patient's vein. *See* JA 46-50.

In 1967, Wyeth advised FDA that it had received a report of a patient who developed gangrene requiring amputation when blood in the patient's arteries came into contact with Phenergan. JA 268-269. At that time, the risk associated with arterial blood exposure to Phenergan was already known, and Phenergan's labeling already warned against intra-arterial injection or perivascular extravasation, which could lead to inadvertent arterial exposure. JA 269.[6]

After the 1967 report, FDA worked closely with Wyeth through a series of communications and meetings to refine Phenergan's warnings with respect to IV administration. In 1973, Wyeth filed a supplemental application seeking approval of certain labeling changes. JA 270. By that time, Phenergan's labeling already advised in two places that intramuscular injection was the "preferred parenteral route of administration." *Id.* The "Dosage and Administration" section stated that "proper intravenous administration . . . is

[6] Perivascular extravasation occurs when a drug intended for intravenous administration escapes from the vein into the surrounding tissue, where it may come into contact with arterial blood. Intra-arterial injection is injection directly into an artery.

well tolerated," but warned that use of this route was "not without some hazard" because, as the labeling noted, "gangrene requiring amputation" could result from exposure of arterial blood to Phenergan through inadvertent intra-arterial injection or perivascular extravasation. JA 276, 277. The "Warnings" section further warned that "[d]ue to the close proximity of arteries and veins in the area most commonly used for intravenous injection, extreme care should be exercised," and specified the maximum concentration and rate of injection for IV administration. JA 276. At FDA's request, Wyeth agreed to add a second statement in the "Warnings" section that IV use of Phenergan was "not without hazard." JA 271, 276.

In 1975, FDA undertook further review of the drug and its labeling. *See* JA 280. As part of that review, Wyeth met with FDA officials to discuss inadvertent intra-arterial injection and other risks of Phenergan and thereafter filed a supplemental NDA to revise Phenergan's labeling. *Id.* FDA responded in May 1976 and instructed Wyeth to make several labeling changes, including adding an upper-case warning that "INT[RA-]ARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY." JA 279-280, 283. FDA also required Wyeth to add an upper-case instruction designed to enhance the safe IV administration of Phenergan: "ASPIRATION OF DARK BLOOD DOES NOT PRECLUDE INTRA-ARTERIAL NEEDLE PLACEMENT AS BLOOD IS DISCOLORED UPON CONTACT WITH PROMETHAZINE." JA 282.[7]

[7] Ordinarily, aspiration of a small amount of blood back into the needle before injection helps determine whether a needle is in

FDA convened an Advisory Committee meeting in October 1976 at which IV administration of Phenergan and the risks arising from arterial blood exposure were again evaluated. *See* JA 287-296. The Committee—composed primarily of medical doctors and researchers—approved the continued contraindication of intra-arterial injection on Phenergan's labeling, JA 289, and proposed a further warning that "[i]f a Tubex system is used for intravenous injection, the drug should be injected into a satisfactorily functioning intravenous set." JA 294.[8] Notably, however, the Committee did not recommend that FDA require Wyeth to eliminate IV administration, including IV push, from the drug's labeling.

In 1979, FDA issued a final rule requiring wholesale updates to the content and formatting of prescription drug labeling for all drugs subject to an approved NDA. *See* 44 Fed. Reg. 37,434 (June 26, 1979). FDA subsequently made clear that labeling changes made to comply with the new regulations "would be subject to prior approval by FDA following the submission of supplemental applications." 45 Fed. Reg. 32,550, 32,550 (May 16, 1980). When Wyeth submitted proposed labeling changes to comply with FDA's general mandate, it stated in its application that the draft labeling was being "submitted for FDA review and approval before

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an artery or a vein because arterial blood is brighter red than venous blood. *See* JA 47. Contact with Phenergan causes discoloration of the blood, however, which makes aspiration an unreliable method of protecting against intra-arterial injection. JA 282, 390.

[8] The Tubex® system described in Phenergan's labeling is a type of injection set that consists of a single-use cartridge preloaded with a dose of Phenergan and a reusable plastic injector. *See* JA 43, 391.

being put into use; no labeling changes, therefore, are to be made at this time." JA 299.

During its review of Wyeth's supplemental application, FDA informed Wyeth that further revisions to Phenergan's labeling "relative to the recognition and management of unintended intra-arterial injection" were under consideration. JA 307-308. By that time, Phenergan's labeling already advised that "[w]hen administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily." JA 324. The labeling also instructed that if a patient complains of pain during IV injection of Phenergan, "the injection should immediately be stopped to provide for evaluation of possible arterial placement or perivascular extravasation." JA 324.

FDA requested several further labeling changes to supplement these statements. JA 309-319. Specifically, FDA instructed Wyeth to revise the existing warning concerning the risk of gangrene from arterial exposure to state that "[t]here are reports of necrosis leading to gangrene, requiring amputation, following injection of [Phenergan]," and to list several instructions for preventing inadvertent intra-arterial injection, including a statement that "[i]njection through a properly running intravenous infusion [set] may enhance the possibility of detecting arterial placement. In addition, this results in delivery of a lower concentration of any arteriolar irritant." JA 311-312. FDA did not withdraw its approval of IV administration of Phenergan or instruct Wyeth to remove IV push administration from the approved methods of administration identified in the labeling.

In 1988, Wyeth submitted a further supplemental application with new proposed labeling that implemented FDA's instructions. *See* JA 334-335. Wyeth's proposal included the following statement: "Injection into an intravenous infusion set that is known to be running properly should decrease the possibility of inadvertently injecting [Phenergan] intra-arterially. In addition, this results in delivery of a lower concentration of any arteriolar irritant." JA 341; *see also* JA 339-340.

In 1997—explaining that it had taken extra time to review Phenergan's proposed labeling changes to ensure that it had "dotted every 'i' and crossed every 't,'" JA 354—FDA ordered Wyeth to make various labeling changes regarding the dosage and administration of Phenergan, JA 355-365, but to "[r]etain verbiage in current label" concerning inadvertent intra-arterial injection, thus rejecting the previously proposed changes, JA 359.[9] Consistent with the FDCA and its implementing regulations, FDA stated that its approval of the supplemental application was contingent on Wyeth implementing these revisions as FDA directed. JA 356, 365. Wyeth accordingly submitted the revised labeling in compliance with FDA's decision, *see* JA 366-380, and FDA approved the revised labeling, JA 381-383. The approval letter advised Wyeth that the final printed labeling "must be identical to the draft package insert" approved in the letter. JA 382.

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[9] FDA identified the "current" labeling as the version Wyeth submitted at FDA's request in August 1996. *See* JA 356 ("current labeling" refers to labeling submitted in August 1996); *see also* JA 346-352 (Wyeth letter to FDA dated August 6, 1996, enclosing then-current labeling).

B. The Labeling In Place When Respondent Was Treated In 2000

As of 2000, following some 45 years of FDA oversight, Phenergan's labeling included repeated, prominent notice—in four separate sections—of the risk of gangrene arising from inadvertent arterial exposure and gave detailed instructions on how to minimize that risk. The "Warnings" section explained:

> Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of Phenergan Injection, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances.

JA 390. The "Adverse Reactions" and "Dosage and Administration" sections each stated in bold, uppercase type: "INTRA-ARTERIAL INJECTION [CAN] RESULT IN GANGRENE OF THE AFFECTED EXTREMITY." JA 391. The "Contraindications" section likewise stated: "Under no circumstances should Phenergan Injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene[.]" JA 390.

To minimize the risk of arterial blood exposure to Phenergan, both the "Contraindications" and "Dosage and Administration" sections advised that "[t]he preferred parenteral route of administration" is "by deep intramuscular injection." JA 390, 391. The labeling

also noted, however, that IV administration was an option, although "not without some hazard." JA 391. To preserve the option of IV administration for those patients who needed it while minimizing the attendant risk, the "Warnings" section instructed:

> When used intravenously, Phenergan Injection should be given in a concentration no greater than 25 mg per mL and at a rate not to exceed 25 mg per minute. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

JA 390. The "Dosage and Administration" section repeated these instructions. JA 391. The "Warnings" section further advised:

> Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with Phenergan Injection. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.

JA 390. This section also instructed that "[i]n the event that a patient complains of pain during intended intravenous injection of Phenergan Injection, the injection should be stopped immediately to provide for evaluation of possible arterial placement or perivascular extravasation." *Id.*

C. Respondent's Treatment With Phenergan

On April 7, 2000, respondent Diana Levine sought treatment at Northeast Washington County Community Health, Inc. (the "Health Center") for a severe migraine headache and associated nausea. JA 18-19, 103;

Pet. App. 2a. Respondent was initially treated with Demerol for the migraine headache and Phenergan for the nausea. JA 19, 38. Both were administered via deep intramuscular injection, the preferred method of administration identified in Phenergan's labeling. *Id.*; Pet. App. 2a.

Respondent returned to the Health Center later that day because she had not obtained effective relief. JA 19, 38-39; Pet. App. 2a. A physician assistant, Jessica Fisch, then administered a second dose of Demerol and Phenergan intravenously by IV push, injecting the medication from a syringe into the tubing of an IV infusion set that led to a needle she had inserted into what she thought was respondent's vein. JA 19, 39, 106.

Fisch testified at trial that she chose to administer the drugs intravenously because the earlier intramuscular injection "hadn't worked at all," and she "felt that in order to give her some relief, that [she] would give it intravenously and try to get it in a more effective and swifter manner." JA 104. Respondent's supervising physician, Dr. John Matthew, testified at trial that IV injection "provides quicker relief" than IM injection and that it would not have been appropriate to administer Phenergan via IM injection once the Demerol was being administered intravenously "[b]ecause the Demerol would be circulating quickly through her brain and potentially causing her to have vomiting while the Phenergan absorbing IM would be slower and delayed so we might have aggravated her nausea and vomiting." JA 41; *see also* JA 40, 60-61.[10]

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[10] Dr. David Greenblatt, a physician and clinical pharmacologist called by the defense, testified that "there are circumstances in which an intramuscular injection is unreliable," including injec-

Although Phenergan's labeling specified a dosage range for nausea of 12.5 to 25 mg, JA 391, Fisch gave respondent a 50 mg dose, *see* JA 105—double the labeled amount. Moreover, Fisch administered the entire 50 mg double dose without pausing, despite respondent's complaints of pain—pain she later described as "one of the most intense pains that [she] had ever felt" to that point, JA 179-181—even though the labeling instructed that IV injection should stop immediately if the patient complains of pain. JA 111, 183, 390. Respondent thereafter developed the symptoms of arterial exposure and gangrene, requiring amputation of her forearm. Pet. App. 2a.

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tions into overweight patients, which may "be injected into fat and be poorly absorbed," and injections into patients who are dehydrated, seriously ill, or suffering from cardiac disease, who may have "poor blood flow to a muscle," which inhibits absorption. JA 200-201. Dr. Thomas Garvey III testified that IV push injection in particular would be appropriate for "[s]omebody who has been vomiting to the point of severe hypobulimia, fluid depletion, veins are very tough to get into" because "[i]f they're vomiting, you want to get in right away, get in, give the drug." JA 195. Dr. Greenblatt further testified:

> [I]t's a judgment that is made by a treating physician who's treating a given patient and, if there is serious distress due to nausea and vomiting, if it won't stop, if the patient is miserable, if the patient is losing fluid and becoming dehydrated and very ill, then the physician in that urgent situation looks at what's available and, with knowing the risks of IV [Phenergan], would nonetheless make a judgment that the benefit to the patient is worthy of accepting that risk.

JA 201.

III. PROCEEDINGS BELOW

A. Trial Court Proceedings

After settling a malpractice suit against Fisch, the Health Center, and the supervising physician, respondent sued Wyeth in a Vermont trial court, alleging state-law claims for inadequate warnings and instructions. Those claims directly challenged FDA's decision to approve labeling that preserved IV administration of Phenergan as an available option for health care providers. The Amended Complaint alleged that Phenergan is

> not reasonably safe for intravenous administration because the foreseeable risks of harm posed by the intravenous administration of the drug are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health care providers, knowing of such foreseeable risks and benefits, would not prescribe the drug intravenously for any class of patients.

JA 15 (¶ 6).

Respondent tried the case under this theory. During opening statements, respondent's attorney claimed that Wyeth "had the obligation to publish instructions that would prevent this from happening. And there was a simple instruction that they could have written[:] 'Do not use this drug intravenously.' That's what the case is about." JA 32; *see also* JA 31. At trial, respondent's expert, Dr. Matthew, asserted, "I think the drug should be labeled 'Not for IV use.' If it were going to be used IV, I think that it should say that it has to be in a running—established IV running at a certain rate." JA 59; *see also* JA 63. Dr. Matthew also testified that "the instructions and warnings and so forth as they're

printed I think are inadequate, insufficient. I don't think the drug should be used IV." JA 65.

Dr. Harold Green, another of respondent's witnesses, also criticized FDA's approval of Phenergan's labeling, testifying that, in his opinion, "somebody at the FDA made an administrative error and approved it." JA 82. In his view, the drug should not have been approved for intravenous administration. JA 79-80. Respondent's FDA expert similarly "disagree[d] with FDA's conclusions" to approve Phenergan's labeling. JA 98. While acknowledging that "FDA knew about the risks associated with this product," JA 97, he claimed that "the benefits do not outweigh the risks" of Phenergan and that "the labeling was inadequate," JA 99, 100.[11] None of respondent's witnesses, nor her counsel, ever contended that Wyeth had any new information about the risks of Phenergan that FDA had

[11] Defense expert witnesses, in contrast, testified that FDA's approval decision was correct and medically sound. One expert disagreed that FDA's 1997 letter directing Wyeth to retain the verbiage in the current label "reflect[ed] an administrative error." JA 189-190. Another expert likewise testified that Phenergan's labeling was adequate and "provide[s] enough instruction to physicians or physician's assistants for the safe use of the product." JA 198-199. He disagreed that "the intravenous use of Phenergan should be banned," JA 200, explaining:

> There are clinical situations in which to produce the needed relief . . . IV may be the preferable or the only way it may be administered. There are obvious risks to IV administration and they are extensively and adequately warned against and, if the treating physician decides that the need to produce relief on that patient is urgent, then it's reasonable to give them the drug IV to produce that relief if it's done properly.

Id.

not already considered in approving Phenergan's labeling.

During closing arguments, respondent's counsel again took issue with Phenergan's FDA-approved labeling, arguing that Wyeth "should have pulled their drug . . . from intravenous use. At a minimum, they should have required that you use a free-flowing IV." JA 211. He also invited the jury to override FDA's labeling approval decision: "Thank God we don't rely on the FDA to . . . make the safe[ty] decision. You will make the decision." *Id.* "The FDA doesn't make the decision, you do." JA 212.

The court's jury instructions likewise invited the jury to disregard FDA's regulatory judgment: "You must decide the extent to which Wyeth should have warned and advised of the risks and injuries which could result from an injection of Phenergan of the type conducted in this case." JA 217. The court reiterated that "[i]t's for you to decide the nature and scope of the warning required," and that "[t]he warning must reasonably advise of the risks and provide adequate instructions to the physician or other medical professional for its safe use." JA 217-218; *see also* JA 220. The jury returned a verdict in favor of respondent and awarded $7.4 million in damages.[12] JA 225-226, 233-235; Pet. App. 3a.

In motions for summary judgment and judgment as a matter of law, Wyeth argued that respondent's claims were preempted. The trial court rejected that argu-

[12] The judgment was adjusted to $6,774,000 to account for prejudgment interest and the settlement in respondent's prior malpractice suit. JA 236; Pet. App. 3a.

ment, ruling that FDA's regulation of labeling sets only minimum standards and thus cannot conflict with additional state-law labeling requirements, and that the FDA's CBE regulation would have permitted Wyeth to strengthen the warnings on Phenergan's labeling without prior FDA approval. JA 21-23, 247-252.

B. Vermont Supreme Court Appeal

On appeal to the Vermont Supreme Court, Wyeth again contended that respondent's claims were preempted because Wyeth could not comply with both its federal duty to distribute Phenergan only under the precise labeling approved by FDA, which permitted IV push administration, and its Vermont common-law duty to alter that labeling to foreclose IV push. Wyeth further argued that enforcing a state-law requirement that foreclosed a method of administration approved by FDA would obstruct Congress's objective of protecting the public health by having an expert agency balance drug risks and benefits and FDA's specific fulfillment of that objective with respect to Phenergan. Pet. App. 6a, 16a, 18a. The Vermont Supreme Court rejected both arguments and affirmed. Pet. App. 19a, 28a, 34a.

The Vermont Supreme Court first held that it would not be impossible for Wyeth to comply with both federal and state-law labeling duties because FDA approval of a drug's labeling is merely a "first step" that sets minimum safety standards, and the CBE regulation "appears to allow unilateral changes to drug labels whenever the manufacturer believes it will make the product safer." Pet. App. 13a, 15a, 17a. The court gave no weight to the comprehensive and mandatory nature of the FDA labeling regime or to FDA's specific directive to Wyeth to "[r]etain verbiage in current label." It held instead that preemption would operate only if

Wyeth could show that FDA would have rejected the precise labeling change sought by respondent. Pet. App. 17a-19a; *see also* Pet. App. 36a-37a.

The court rejected Wyeth's claim that the state-law duty underlying respondent's suit would obstruct the objectives of FDA's regulatory regime. In the court's view, all such "obstacle" preemption claims were foreclosed by language in the 1962 amendments to the FDCA that limited preemption claims arising from those amendments to cases of "'direct and positive conflict between such amendments and [a] provision of State law.'" Pet. App. 21a (quoting Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. at 793). The court reasoned that "direct and positive conflict[s]" denoted only those conflicts giving rise to "impossibility" preemption and thus "remove[d] from [its] consideration the question of whether common-law tort claims present an obstacle to the purposes and objectives of Congress." Pet. App. 21a; *see also* Pet. App. 21a-24a.

Chief Justice Reiber dissented, concluding that "compliance with state law in this case would require Wyeth to eliminate uses of Phenergan approved by the FDA and required to be included in the Phenergan labeling." Pet. App. 35a. He explained that "FDA clearly addressed the risks attending IV administration of the drug[,] . . . approved IV administration generally, and specifically warned of the dangers of direct IV administration, including inadvertent arterial injection possibly resulting in amputation." Pet. App. 38a. "These assessments are, in fact, the very essence of the FDA's approval and are in furtherance of the federal objective of advancing public health by balancing the risks and benefits of new drugs and facilitating their optimal use." *Id.* A jury's consideration of drug safety "through the lens of a single patient who has already

been catastrophically injured," in contrast, "is virtually guaranteed to provide different conclusions in different courts about what is 'reasonably safe' than the balancing approach taken by the FDA." Pet. App. 48a. He further concluded that respondent sought a labeling change "that would directly contradict language approved and mandated by the FDA," and that the CBE regulation would not have permitted Wyeth to change Phenergan's labeling in the manner respondent sought. Pet. App. 39a-40a.

SUMMARY OF ARGUMENT

It is well established that "state law that conflicts with federal law is without effect." *Cipollone* v. *Liggett Group, Inc.*, 505 U.S. 504, 516 (1992) (internal quotation marks omitted). Respondent's state-law tort claims conflict with the regime Congress established in the FDCA in two ways.

First, it would have been impossible for Wyeth to comply with the purported state-law duty to modify Phenergan's labeling to contraindicate intravenous administration of Phenergan without violating the FDCA. State law conflicts with federal law and is preempted "when compliance with both federal and state regulations is a physical impossibility." *Fidelity Fed. Sav. & Loan Ass'n* v. *de la Cuesta*, 458 U.S. 141, 153 (1982) (internal quotation marks omitted). Under the FDCA, FDA's approval of a drug's labeling is inextricably intertwined with its approval of the drug itself. The approval process requires FDA to determine whether a new drug is safe and effective under the conditions set forth in the labeling. FDA must also determine whether the labeling satisfies the comprehensive and detailed requirements of federal law, and its ultimate approval of a new drug is conditioned on the manufac-

turer's adopting any changes to the labeling exactly as FDA directs. Once approved, therefore, the labeling ordinarily may not be modified without FDA authorization, and Wyeth would have violated the FDCA had it changed Phenergan's labeling in the manner required by respondent's claims.

The Vermont Supreme Court's contrary conclusion rested on an erroneous interpretation of an FDA regulation that governs when labeling changes may be put into temporary effect without prior FDA approval. As properly construed by FDA, that regulation establishes a limited safe harbor from enforcement for manufacturers that implement labeling changes prior to FDA approval when the change reflects newly acquired information about a drug's risks. That reading is supported by the history of the regulation and its relationship to the purposes of the FDCA as a whole; it is also the interpretation that FDA has reasonably advanced. In this case, respondent has never suggested that Wyeth had any new information about the risks of IV administration of Phenergan that would have warranted a change without FDA approval. Rather, when FDA approved the Phenergan labeling that was in place when respondent was injured, it did so with full information about the risks and benefits of the drug, and it instructed Wyeth to use labeling that FDA had concluded best accommodated those risks and benefits. Wyeth was not permitted to depart from FDA's conclusion—as state law would have required—without violating the FDCA and FDA's regulations.

Respondent's claims are also preempted for the independent reason that they "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hines* v. *Davidowitz*, 312 U.S. 52, 67 (1941). In the FDCA, Congress established

a regime in which an expert agency approves a new drug for distribution under specifically reviewed labeling, based on particularized judgments about the relative risks and benefits of that new drug. Those judgments advance the overall public health by recognizing that the benefits of a particular treatment for certain patients can justify the approval of a drug for uses consistent with its labeling even where its use may also present risk of harm. To minimize risk while preserving the availability of beneficial treatments, FDA reviews the warnings and other information on a drug's labeling and seeks to manage the relevant risks by specifying the information it concludes is necessary to advise users how to use the drug safely and effectively. Thus, contrary to the Vermont Supreme Court's conclusion, the regime Congress created does not establish mere minimum safety standards that a State may freely supplement without limit, but strikes a balance between often competing objectives. FDA carried out Congress's intent by approving labeling for Phenergan that recognized IV injection as a permissible option for health care providers in light of its superior efficacy and speed of relief while providing detailed information on the risks of IV injection and how to avoid them.

Vermont law, in contrast, would displace FDA's expert judgment and substitute the verdicts of lay jurors in fifty States who consider drug safety after the fact on a case-by-case basis, focusing on a single patient's catastrophic injury, rather than the potential benefits of the drug to the public as a whole—an approach that inherently will produce risk-averse determinations. Moreover, respondent's state-law claims interfere with FDA's fulfillment of Congress's intent in the case of Phenergan by second-guessing FDA's determination that, with appropriate warnings and in-

structions on the labeling, the benefits of IV administration of Phenergan outweigh the well-known risk of harm. Because recognition of the state tort action in this case would frustrate the purposes of federal law both by substituting the verdicts of lay juries for the expert balancing Congress directed FDA to conduct and by upsetting the particular balance FDA struck with respect to Phenergan, respondent's claims are preempted.

ARGUMENT

Article VI of the Constitution makes "the Laws of the United States . . . the supreme Law of the Land." U.S. Const. art. VI, cl. 2. "[T]he Supremacy Clause invalidates all state laws that conflict or interfere with an Act of Congress." *Rose* v. *Arkansas State Police*, 479 U.S. 1, 3 (1986) (per curiam). Such a conflict arises "when compliance with both federal and state regulations is a physical impossibility," or when "state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Fidelity Fed. Sav. & Loan Ass'n* v. *de la Cuesta*, 458 U.S. 141, 153 (1982) (internal quotation marks omitted). Respondent's state-law claims present both types of conflict and are therefore preempted.

I. Respondent's Claims Are Preempted Because It Is Impossible For Wyeth To Comply With Both The State-Law Duties Those Claims Impose And Its Federal Labeling Duties

The FDCA required Wyeth to distribute Phenergan only with the labeling that FDA had approved. FDA's CBE regulation did not permit any modification to the labeling in the absence of newly acquired risk information, which did not exist in this case. Vermont

law, by contrast, imposed a tort-law requirement that Wyeth alter that labeling to foreclose IV administration, or at least IV push injection. Because these two commands are irreconcilable, Vermont law must yield.

A. The FDCA And Vermont Law Imposed Irreconcilable Requirements On Wyeth

FDA's approval of a new drug reflects the agency's definitive judgment that a drug is safe and effective under the conditions of use identified in the drug's labeling, and that the drug as so labeled may lawfully be distributed in interstate commerce. Under this regime, Wyeth was required to distribute Phenergan only with the labeling that FDA had approved. Had Wyeth unilaterally altered the labeling to change the warnings with respect to arterial blood exposure or to eliminate IV push as an approved method of administration, it would have been in violation of federal law and subject to enforcement action by FDA for unauthorized distribution or misbranding. *See* 21 U.S.C. §§ 331(a), (d), 333(a), 334(a), 352, 355(a), (d); 21 C.F.R. § 314.105(b).

As discussed, *supra* pp. 8-10, FDA review of a New Drug Application is a rigorous process that focuses on whether the drug is safe and effective under the labeled conditions of use and whether its labeling complies with extensive and detailed regulations. FDA approval of a drug's labeling is thus part and parcel of its approval of the drug itself. Indeed, should FDA find any deficiencies in the proposed labeling during its review of an NDA, FDA will specify exactly how those deficiencies should be corrected; final approval of the NDA is "conditioned upon the applicant incorporating the specified labeling changes exactly as directed." 21 C.F.R. § 314.105(b).

With limited exceptions discussed below, a manufacturer may not make any changes to a drug after it has been approved, including changes in labeling, without submitting a supplemental application and obtaining FDA's prior approval. 21 C.F.R. § 314.70(b)(1), (b)(2)(v)(A), (b)(3). Federal law thus required Wyeth to submit any proposed change in Phenergan's labeling for FDA review and prohibited Wyeth from implementing that change without FDA's approval.

Similar features of FDA's premarket approval of Class III medical devices recently led this Court to find preemption of state-law tort claims in that analogous context. *Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999 (2008). In *Riegel*, the Court held that once a Class III medical device receives premarket approval, the FDCA (as amended by the Medical Device Amendments of 1976 (MDA)) forbids the manufacturer to make any change without FDA permission, including a change to the approved labeling, that would "affect safety or effectiveness." *Id.* at 1005. Any change must be submitted by supplemental application for FDA approval before implementation. *Id.* The Court thus held that FDA's detailed, individualized review of the safety and effectiveness of each Class III medical device imposed a federal-law "requirement" that approved devices be made "with almost no deviations from the specifications in its approval application," and preempted conflicting state-law requirements applicable to the device. *Id.* at 1006-1007.

The same holds true for prescription drugs, which are subject to an approval process that is closely similar

to the MDA's premarket approval process.[13] For both drugs and Class III devices, manufacturers must submit full reports of investigations showing whether the product is safe and effective as well as specimens of the proposed labeling. *Compare* 21 U.S.C. § 355(b)(1) (drugs) *with id.* § 360e(c)(1) (devices). In both instances, FDA conducts a detailed, individualized review of the product and is required to deny approval if that product has not been shown to be safe and effective for "use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." *Compare id.* § 355(d) (drugs) *with id.* § 360e(d)(2) (devices). And in both instances, the manufacturer may not make "changes in labeling" without first submitting a supplemental application and obtaining FDA approval, except under narrow circumstances not implicated here. *Compare* 21 C.F.R. § 314.70(b)(1), (b)(2)(v)(A), (b)(3), (c)(6)(iii) (drugs) *with id.* § 814.39(a)(2), (d)(1), (d)(2)(i)-(iii) (devices).[14]

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[13] Indeed, the premarket approval process for medical devices was modeled on the NDA process for approval of new drugs. *See* H.R. Rep. No. 94-853, at 16 (1976) (FDA authority to regulate safety and effectiveness of devices "is derived from drug law"); *id.* at 17 (standard for determining effectiveness of devices is "derived from existing provisions of the [FDCA] relating to drugs"); H.R. Conf. Rep. No. 94-1090, at 62 (1976) (placing devices previously regulated as drugs into "comparable regulatory status" under device law); 21 U.S.C. § 360j(*l*)(3)(A)(ii) ("[R]equirements applicable to [Class III] device[s] before the enactment date under [the NDA provision] shall continue to apply to such device[s]."); *see also* U.S. Br. 9 ("FDA's review of a new drug application is similar to its premarket approval process for Class III medical devices[.]").

[14] Like premarket approval of Class III medical devices, FDA's review of New Drug Applications thus stands in sharp contrast to the "substantial equivalence" review at issue in *Medtronic*,

Federal law thus required Wyeth to distribute Phenergan only with the FDA-approved labeling, which preserved IV injection, including by IV push, as an approved method of administration. Consistent with that requirement, FDA's 1997 letter to Wyeth approving the Phenergan labeling in place at the time of respondent's injury instructed that "[t]he final printed labeling . . . must be identical to" the FDA-approved draft version. JA 382.

The Vermont verdict in this case, to the contrary, rested on a state-law duty to change that labeling to eliminate the option of IV administration, or, at a minimum, IV push. No less than a state statute or regulation, this common-law claim is preempted if it imposed a duty that conflicts with federal law. *See Riegel*, 129 S. Ct. at 1007-1008 ("[C]ommon-law liability is premised on the existence of a legal duty, and a tort judgment therefore establishes that the defendant has violated a state-law obligation." (internal quotation marks omitted)); *see also Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 350-353 (2001); *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 881-886 (2000). Here, Wyeth could not have complied with both its federal and Vermont duties. In these circumstances, the federal duty under the FDCA must prevail. *See, e.g.*, *Crosby* v. *National Foreign Trade Council*, 530 U.S. 363, 372 (2000) ("We will find preemption

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Inc. v. *Lohr*, 518 U.S. 470 (1996), under which FDA enforces only generally applicable labeling requirements that "reflect[] 'entirely generic concerns about device regulation generally'" and involve no device-specific review for safety and efficacy. *See Riegel*, 128 S. Ct. at 1006-1007 (quoting *Lohr*, 518 U.S. at 501).

where it is impossible for a private party to comply with both state and federal law[.]").

B. The Vermont Court Misinterpreted The CBE Regulation

The Vermont Supreme Court conceded that this case might be "very different" if federal law required Wyeth to use only FDA-approved labeling. Pet. App. 10a. It held, however, that FDA's CBE regulation, 21 C.F.R. § 314.70(c)(6)(iii), eliminated the conflict between federal and Vermont law by allowing a manufacturer to make "unilateral changes to drug labels," without obtaining prior approval, "whenever the manufacturer believes it will make the product safer." Pet. App. 13a. This construction of FDA's regulations is wrong. The CBE regulation permits labeling changes only when the change reflects newly discovered information about a drug's safety that was not previously considered by FDA. Because respondent has not shown or even alleged that Wyeth had any such information concerning the risks of IV administration of Phenergan, the CBE regulation would not have permitted Wyeth to make the labeling changes that respondent's tort suit required.

As discussed, Congress required FDA to review individual drug labeling as part of the NDA process and to hold manufacturers to that approved labeling. Congress did this by expressly tying FDA review and approval of a drug to the labeling under which that drug would be distributed and by making the labeling itself a required and central part of the NDA. *See* 21 U.S.C. § 355(a), (b)(1)(F), (c)(1)(A), (d). Allowing a manufacturer to alter that labeling unilaterally in a manner that affects safety or effectiveness—when it has no material new information that was not available to FDA, but

simply disagrees with how FDA exercised its expert judgment with respect to a risk of which it was fully aware—would undermine the core premise upon which FDA approval of the drug is conditioned: the determination that the drug is safe and effective *as labeled*, *id.* § 355(d). Moreover, alteration of labeling departs from the NDA, making the drug an unauthorized "new drug" for which no NDA is effective; its shipment in interstate commerce would therefore be expressly forbidden by the FDCA. *Id.* § 355(a); *see also id.* §§ 321(p), 331(d). As interpreted by the Vermont Supreme Court, the CBE regulation would thus be so inconsistent with the drug approval scheme established by the FDCA that its promulgation would likely lie outside FDA's statutory authority. *Cf. FDA* v. *Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 125 (2000) (FDA "may not exercise its authority in a manner that is inconsistent with the administrative structure that Congress enacted into law" (internal quotation marks omitted)); *Board of Governors of Fed. Reserve Sys.* v. *Dimension Fin. Corp.*, 474 U.S. 361, 374 (1986) (agency's "rulemaking power is limited to adopting regulations to carry into effect the will of Congress as expressed in the statute").

The history of the CBE regulation demonstrates that it was never intended to carry the broad meaning the Vermont Supreme Court attributed to it. The 1938 FDCA made no provision for changes to approved labeling. In 1944, FDA by regulation provided for labeling changes, but made clear that they could be effected only if a manufacturer filed a supplemental application and obtained FDA's approval prior to implementing the change. 9 Fed. Reg. 12,255, 12,256 (Oct. 10, 1944). In 1956, FDA amended the regulation to make the preapproval requirement even more explicit, providing

that "[a] supplemental application should be submitted for any change . . . that may alter . . . the labeling," and that "[i]f a material change is made from the representations in an effective application for a new drug before a supplement is effective for such change, the application may be suspended." 21 Fed. Reg. 5576, 5579 (July 25, 1956). Suspension would prohibit further distribution of the drug in interstate commerce. *See* 21 U.S.C. § 355(a).

To allow labeling changes reflecting new drug safety information to be "placed into effect at the earliest possible time," FDA issued the predecessor to the current CBE regulation in 1965. 30 Fed. Reg. 993 (Jan. 30, 1965). The regulation provided that a manufacturer could submit a supplemental application proposing certain kinds of labeling changes, and then implement those changes without waiting for FDA approval, if the manufacturer notified FDA that the change was being effected and gave a full explanation of the basis for the proposed change. *Id.* at 993-994. Permissible changes included the addition of "additional warning, contraindication, side-effect, and precaution information." *Id.* Although, as FDA made clear, distribution of the drug without prior FDA approval of the labeling change would be unlawful, FDA stated that it would not pursue sanctions against manufacturers who changed labeling only to include new or strengthened cautionary material based on new safety information:

> It will be the policy of the Food and Drug Administration to take no action against a drug or applicant solely because changes of the kinds described in . . . this section are placed in effect by the applicant prior to his receipt of a written notice of approval of the supplemental new-drug application[.]

Id. at 994. The regulation was thus an exercise of FDA's enforcement discretion under the FDCA, intended to enable prompt adoption of changes needed "in the interest of drug safety." *Id.* at 993. FDA warned, however, that nothing in the regulation limited FDA's ultimate authority to suspend or withdraw approval of an NDA or take action against a drug or manufacturer that otherwise violated the FDCA. *Id.* at 994.

In 1982, FDA proposed to revise the CBE regulation into what is effectively its present form. The proposal explained that the regulation applied to changes made "to correct concerns about *newly discovered* risks from the use of the drug" and to "make available important *new information* about the safe use of a drug product." 47 Fed. Reg. 46,622, 46,623, 46,635 (Oct. 19, 1982) (emphases added). All other labeling changes, except minor, editorial revisions, remained subject to the prior approval requirement. *Id.* at 46,635.[15] FDA adopted the revised regulation in 1985. 50 Fed. Reg. 7452, 7498-7499 (Feb. 22, 1985). In promulgating the final CBE rule, FDA explained that the category of labeling changes that could be made without prior FDA approval had to be narrow because "[s]ubstantive changes in labeling . . . are more likely than other

[15] These statements were consistent with FDA's earlier statements about the CBE regulation. Though FDA had said in 1979 that its regulations did not prohibit labeling changes made to add or strengthen warnings without prior FDA approval, 44 Fed. Reg. 37,434, 37,447 (June 26, 1979), it maintained the view at that time that such changes were permissible "whenever possibly harmful adverse effects associated with the use of the drug are discovered," *id.*, suggesting that only changes reflecting newly acquired risk information would be permitted.

changes to affect the agency's previous conclusions about the safety and effectiveness of the drug." *Id.* at 7470.

Consistent with this history, FDA has recently made clear that the CBE regulation provides only a "limited exception" to the general rule requiring prior approval of labeling changes. U.S. Br. 13. As the Solicitor General and FDA have explained, the CBE regulation is properly read to permit labeling changes without prior approval only when the change is "based on material new information—not information that was previously available to FDA, nor even cumulative new information that does not add materially to the information that was previously available to the agency." *Id.* 14. Even then, FDA retains authority to approve or reject the change, and to take enforcement action against any change that results in misbranding. *Id.* at 15. For this reason, "in practice manufacturers typically consult with FDA before making labeling changes" under the CBE regulation. *Id.*

Earlier this year, FDA reaffirmed this interpretation in a proposed rulemaking. 73 Fed. Reg. 2848, 2850 (Jan. 16, 2008) (defining information appropriate for CBE supplement as "data, analyses, or other information not previously submitted to the agency, or submitted within a reasonable time period prior to the CBE supplement, that provides novel information about the product, such as a risk that is different in type or severity than previously known risks about the product"). Reviewing the history of the CBE regulation, FDA stated that its proposal would "codify the agency's longstanding view" on when labeling changes may be effected without prior approval—namely, when necessary "only to reflect newly acquired information." *Id.* at 2848-2850.

FDA's interpretation of its CBE regulation as a limited exception applicable only where newly acquired, scientifically significant information requires an immediate response is "controlling unless plainly erroneous or inconsistent with the regulation." *Auer* v. *Robbins*, 519 U.S. 452, 461 (1997) (internal quotation marks omitted); *see also Federal Express Corp.* v. *Holowecki*, 128 S. Ct. 1147, 1155 (2008) (deferring to agency's "permissible reading" of its own regulation, where regulation's scope was "less than clear"; agency is entitled to deference "when it adopts a reasonable interpretation of regulations it has put in force"). Deference is particularly appropriate here, where the regulation reflects the agency's exercise of specifically delegated discretion to enforce a complex regulatory scheme. *See Heckler* v. *Chaney*, 470 U.S. 821, 835 (1985) (FDCA's enforcement provisions "commit complete discretion to [FDA] to decide how and when they should be exercised"); *see also id.* at 831-832; *Chevron U.S.A. Inc.* v. *Natural Res. Def. Council, Inc.*, 467 U.S. 837, 865 (1984).

In this case, the CBE regulation—properly construed—did not permit Wyeth to deviate from Phenergan's FDA-approved labeling without prior FDA approval. While a different issue might have been presented had Wyeth learned of significant new risk information not presented to FDA, respondent has never suggested that Wyeth acquired any such new information, or that FDA was not already completely aware of all the risks. Indeed, respondent's counsel argued the opposite, stating to the jury that reports of adverse events associated with arterial blood exposure to Phenergan have existed "since at least 1969," and that "these reports are in the FDA database." JA 31. Respondent's expert similarly conceded that "FDA knew

about the risks associated with this product." JA 97. In these circumstances, Wyeth had no good-faith basis to invoke the CBE regulation, and it would have been impossible for Wyeth to comply with the state-law duty underlying respondent's claims by changing Phenergan's labeling to contraindicate use of IV push injection without violating these federal requirements. The claims are therefore preempted.

II. Requiring Wyeth To Comply With A State-Law Duty To Foreclose IV Push Administration Would Obstruct The Purposes And Objectives Of The Act And Its Implementation By FDA

State law is preempted when it "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hines*, 312 U.S. at 67. In the FDCA, Congress established a drug-approval regime in which an expert scientific agency makes uniform, national judgments about the safety and effectiveness of prescription drugs by balancing therapeutic benefits against safety risks *ex ante*, taking into account the interests of all potential patients. FDA struck precisely that type of balance in approving IV administration of Phenergan and in determining what warnings and instructions were appropriate to manage its associated risks. Vermont, by contrast, seeks to alter that balance by substituting the judgment of lay juries that focus on individual patients' injuries on a case-by-case basis, effectively disregarding the countervailing benefits of the drug to the public as a whole. *See Riegel*, 128 S. Ct. at 1008. The Vermont judgment thus frustrates both Congress's objective of having an expert agency serve as the ultimate regulator of the labeled conditions of use for which a drug is approved and FDA's specific fulfillment of that objective in establishing an elaborate and balanced network

of cautions and instructions on Phenergan's labeling with respect to the risks of IV administration. Respondent's claims are therefore preempted.[16]

A. Congress Mandated FDA To Make Particularized, Labeling-Specific Decisions That Balance Competing Considerations To Advance The Public Health

In determining whether a state law interferes with the full purposes and objectives of Congress, courts consider "the entire scheme of the statute"—its text, its context, and the policies underlying it. *Hines*, 312 U.S. at 67 n.20. Here, the regulatory scheme Congress established provides that FDA's drug-approval and labeling decisions must strike a balance between protecting the public from dangerous misuses of drugs and advancing public health by ensuring that beneficial treatments are available to those who need them.

Congress placed responsibility for resolving the tension between these competing objectives in an expert federal agency. In general, FDA regulation serves the dual objectives of protecting the public from dangerous products and promoting public health by facilitating access to beneficial treatments. *See* 21 U.S.C. § 393(b) (requiring FDA to "protect the public health by ensuring that . . . drugs are safe and effective" and to "promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a

[16] This case does not present the question whether the FDCA preempts claims that do not implicate labeling, such as manufacturing defect claims. Accordingly, Wyeth confines its argument to the preemptive effect of the Act's labeling requirements and FDA's implementation of those requirements.

timely manner"). These objectives are particularly relevant in the context of drug labeling, which serves as the "centerpiece of risk management" and "communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." 71 Fed. Reg. at 3934.

Labeling decisions require an understanding of what information a physician or other health care provider needs in order to make informed judgments about what course of treatment is appropriate for a particular patient. FDA must take account of the known risks and benefits of each condition of use for which a drug is labeled and carefully regulate that labeling to ensure that it includes the right balance of warnings and instructions that promotes beneficial use of the drug while minimizing associated risks. "[A]dditional requirements for the disclosure of risk information are not necessarily more protective of patients" because "[e]xaggeration of risk could discourage appropriate use of a beneficial drug." 71 Fed. Reg. at 3935.

Congress thus required a scientific review process presided over by an expert agency that assesses the risk-benefit profile of a drug under labeled conditions of use and actively manages that labeling to ensure that it advances the drug's safe and beneficial use.[17] FDA's

[17] FDA's oversight of prescription drug labeling is thus very different from the role played by the Environmental Protection Agency with respect to pesticide labeling. As this Court explained in *Bates* v. *Dow Agrosciences LLC*, 544 U.S. 431 (2005), although EPA reviews pesticide labels to ensure against misbranding, EPA does not conduct individualized review of the efficacy of individual pesticides or confirm efficacy claims on a pesticide's labeling. *See id.* at 440 ("EPA's approval of a pesticide label does not reflect any

scientific judgment on these issues warrants deference. *See, e.g.*, *Weinberger* v. *Bentex Pharms., Inc.*, 412 U.S. 645, 653-654 (1973) ("[t]he determination whether a drug is generally recognized as safe and effective . . . necessarily implicates complex chemical and pharmacological considerations" and is "peculiarly suited to initial determination by the FDA."); *Nutraceutical Corp.* v. *Von Eschenbach*, 459 F.3d 1033, 1043 (10th Cir. 2006) ("The review of scientific literature is properly in the province of the FDA, to which this Court grants deference based on its expertise."), *cert. denied*, 127 S. Ct. 2295 (2007); *Schering Corp.* v. *FDA*, 51 F.3d 390, 399 (3d Cir. 1995) ("[FDA's] judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us.").

FDA carried out this obligation to balance competing objectives in the specific case of Phenergan. In approving Wyeth's supplemental application in 1997, as it had in its prior Phenergan labeling actions, FDA sought to maximize Phenergan's therapeutic benefit by balancing the well-known and clearly labeled risk of inadvertent arterial exposure against the benefit of more potent and expeditious anti-nausea relief. On the one hand, intravenous injection of Phenergan offers unique benefits relative to other forms of administration and is

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determination on the part of EPA that the pesticide will be efficacious or will not damage crops or cause other property damage." (internal quotation marks omitted)). For example, in the dispute before the Court in *Bates*, "EPA never passed on the accuracy of the statement" in the labeling challenged in that case. *Id.* Under the FDCA, in contrast, a drug's labeling is central to FDA's review of the safety and efficacy of the drug, and FDA carefully monitors the content and format of each drug's labeling.

the most effective medicine for some patients. *See supra* nn. 10, 11; JA 40-41, 104, 194-195, 200-201. On the other hand, there is a risk that human error during IV injection of Phenergan will cause arterial exposure resulting in serious injury to the patient. Rather than require the contraindication of IV administration altogether (or even just IV push), FDA approved labeling that maintained IV injection as an approved method of administration and managed the attendant risk through a carefully tailored set of warnings and instructions. FDA thus concluded that the network of limitations and warnings in Phenergan's labeling appropriately warned users of the serious risks of IV injection—risks of which FDA was fully informed—and provided information on how IV administration could be done safely.

The Vermont Supreme Court thought that the overriding objective of the FDCA was solely to protect consumers from dangerous products, Pet. App. 20a, and that FDA's approval of a drug and its labeling was therefore nothing more than "a first step in the process of warning consumers," Pet. App. 15a. On that view, federal law sets only minimum safety standards that manufacturers may freely supplement with unlimited additional warnings. Pet. App. 20a. The court thus concluded that a state law requiring manufacturers to add further warnings beyond what FDA required, or to contraindicate methods of administration that FDA had approved as safe and effective, poses no problem under the FDCA because such a requirement would serve the same purpose as federal law—namely, to "encourag[e] pharmaceutical companies to alter their drug labels when they are inadequate to protect consumers." Pet. App. 15a.

As an initial matter, that reasoning is wrong in this case because FDA concluded that Phenergan's labeling

was *not* "inadequate to protect consumers." Pet. App. 15a. Rather, FDA's approval of the 1997 supplemental application indicated its determination that Phenergan was safe and effective under the labeled conditions of use, including use by IV injection. 21 U.S.C. § 355(d). More fundamentally, however, the Vermont Supreme Court erred in concluding that Congress's sole objective in the FDCA was to protect consumers from dangerous products, and that federal requirements therefore constitute only minimum safety standards.[18] The regulatory scheme that Congress established in the FDCA and that FDA implemented in the specific case of Phenergan serves competing goals: to protect the public from unreasonable risk of harm, while ensuring the availability of beneficial treatments, all of which carry a certain degree of risk. *See supra* pp. 7-8, 41-42; *see also Riegel*, 128 S. Ct. at 1009. And an approved drug's labeling must provide sufficient instructions for safe and effective use, while avoiding limitations that foreclose beneficial use of a drug in an effort to avoid all risk of human error. For these reasons, as the United States has explained, "'FDA interprets the [FDCA] to establish both a "floor" and a "ceiling"' with respect to drug labeling," U.S. Br. 11 (quoting 71 Fed. Reg. at 3935) (alteration in U.S. Br.), and "FDA's approval of labeling for a new drug reflects FDA's expert judgment that the labeling strikes the appropriate balance,"

[18] In any event, even if state and federal law share the same ultimate goal, state law is still preempted if it "interferes with the methods by which the federal statute was designed to reach this goal." *International Paper Co.* v. *Ouellette*, 479 U.S. 481, 494 (1987). "The fact of a common end hardly neutralizes conflicting means[.]" *Crosby*, 530 U.S. at 379.

id. The Vermont Supreme Court erred in concluding otherwise.

B. The Vermont Judgment Conflicts With Congress's Public-Health Objectives

Respondent's state-law claims frustrate the public-health objectives underlying the FDCA—and FDA's implementation of the FDCA in the case of Phenergan—by interfering with Congress's purpose to entrust an expert agency to make drug labeling decisions that strike a balance between competing objectives. Pursuant to Congress's mandate, FDA made an expert judgment that the benefits of a speedier and more potent method of administration outweighed the risks associated with IV administration of Phenergan, and that the labeling properly explained the risks and how to avoid them and thus should be retained. FDA based that judgment on its assessment of the overall public health. Under Vermont law as applied below, in contrast, a single lay jury reweighs those risks and benefits, focusing not on the public health as a whole, but on the harm suffered by a single patient. As this Court observed in *Riegel*, a jury "sees only the cost of a more dangerous design, and is not concerned with its benefits; the patients who reaped those benefits are not represented in court." 128 S. Ct. at 1008. As such, juries will be systematically more risk-averse, which can undermine the public health by leading manufacturers to include excessive warnings on labeling or to remove effective methods of administration from the labeling.[19]

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[19] Chief Justice Reiber made a similar point in dissent below, noting that "the jury does not assess reasonableness in the context of public health and the associated risk-benefit analysis," but rather "views the safety of the drug through the lens of a single

This Court has made clear that where federal law strikes a balance between competing objectives, "that is not a judgment the States may second-guess." *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 152 (1989). Rather, state regulation "must yield to the extent that it clashes with the balance struck by Congress." *Id.* Thus, in *Geier* v. *American Honda Motor Co.*, 529 U.S. 861 (2000), this Court held that state tort law was preempted to the extent that it reached a different balance among several competing objectives than the balance the federal policy had struck. *Id.* at 874-881.

This case presents a conflict between state and federal law analogous to the one the Court addressed in *Geier*. The federal safety regulation at issue in *Geier* "deliberately provided the manufacturer with a range of choices among different passive restraint devices," which "would bring about a mix of different devices introduced gradually over time." 529 U.S. at 864-865, 875. The goal of the federal scheme was not to set minimum airbag standards—seeking "the more airbags, and the sooner, the better," *id.* at 874—but to accommodate multiple competing concerns, *id.* at 875. This Court held that the federal objective preempted the alleged tort duty because the duty "would have presented an obstacle to the variety and mix of devices that the federal regulation sought" and "stood as an obstacle to the general passive restraint phase-in that the federal regulation deliberately imposed." *Id.* at 881.

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patient who has already been catastrophically injured," an approach that "is virtually guaranteed to provide different conclusions in different courts about what is 'reasonably safe' than the balancing approach taken by the FDA." Pet. App. 48a.

Here, as in *Geier*, FDA balanced competing concerns of safety and therapeutic benefit by considering the risks of IV administration of Phenergan and preserving the option for physicians to administer Phenergan by IV push in appropriate cases, subject to carefully crafted warnings and instructions in the labeling. Vermont sought to foreclose that option here by basing a damage award on its availability, an award imposed by a lay jury that reconsidered the precise risk information FDA had already weighed. Thus, just as in *Geier*, respondent's claims stand as an obstacle to the accomplishment and execution of federal objectives and are preempted.[20]

In contrast, this Court has rejected preemption claims in cases where federal law did not impose particularized requirements that reflected an accommodation of competing concerns. In *Medtronic, Inc.* v. *Lohr*, 518 U.S. 470 (1996), for example, the Court held that

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[20] *See also Buckman*, 531 U.S. at 348-350 (holding state tort claims challenging manufacturer's fraudulent misrepresentations to FDA to be preempted because they threatened to "skew[]" the "balance sought by [FDA]" in exercising its options to punish and deter fraud and thus would "inevitably conflict" with FDA's statutory responsibilities); *Barnett Bank of Marion County, N.A.* v. *Nelson*, 517 U.S. 25, 31, 37 (1996) (finding preemption where state law prohibited activities that federal law authorized); *Ouellette*, 479 U.S. at 494-497 (state law that "upset[] the balance of public and private interests so carefully addressed" by federal statute and that potentially undermined "Congress's considered judgment as to the best method of serving the public interest and reconciling . . . often competing concerns" was preempted); *de la Cuesta*, 458 U.S. at 156 (by "limiting the availability of an option" the federal agency considered essential to its objectives, state created an "obstacle to the accomplishment and execution of the full purposes and objectives" of federal law (internal quotation marks omitted)).

the "substantial equivalency" regime for FDA approval of certain medical devices did not preempt common-law claims because the approval process reflected only general concerns about device regulation, not particularized determinations about the safety and effectiveness of specific devices. *Id.* at 501. The case was thus "quite unlike a case in which the Federal Government has weighed the competing interests relevant to the particular requirement in question, reached an unambiguous conclusion about how those competing considerations should be resolved in a particular case or set of cases, and implemented that conclusion via a specific mandate on manufacturers or producers." *Id.*[21] FDA's approval of Phenergan's labeling, in contrast, constitutes precisely the kind of case distinguished in *Lohr*: FDA considered and resolved the competing considerations relevant to IV administration of Phenergan and implemented that decision by requiring Wyeth to distribute the drug only with specified labeling.

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[21] *See also Riegel*, 128 S. Ct. at 1006-1007; *supra* n.14. This Court's decision in *Sprietsma* v. *Mercury Marine*, 537 U.S. 51 (2002), is similarly distinguishable. There, the Court found no preemption because the Coast Guard had decided to take no regulatory action at all on the question whether boats should be equipped with propeller guards. Contrary to the federal government's position in *Geier*, the Coast Guard in *Sprietsma* made clear that it perceived no conflict between state-law boat safety requirements and the federal regulatory scheme under the Federal Boat Safety Act, which expressly described the Coast Guard's regulations as setting "minimum safety standards." *Id.* at 58 n.6, 67-68. And unlike FDA's particularized review of each prescription drug it approves, the Coast Guard in *Sprietsma* did not undertake to "certify the acceptability of every recreational boat subject to its jurisdiction." *Id.* at 69.

Consistent with this conclusion, FDA has explained that, in its view, a state-law requirement that a manufacturer include additional warnings, instructions, or other information on a drug's labeling beyond what FDA has required would upset the balance struck under federal law between drug risks and benefits. 71 Fed. Reg. at 3934-3936. By requiring labeling to rule out methods of administration or other uses that FDA has approved, or to include excessive warnings and cautionary material sufficient to appease a risk-averse jury, a state-law duty to warn "can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use" and "discourage appropriate use of a beneficial drug," thereby "undermining the objectives of the act." *Id.* at 3935.[22] Thus, because respondent's claims frustrate the purpose of the FDCA's labeling requirements and stand as an obstacle to the

[22] As this Court observed in *Geier*, where Congress has delegated authority to an expert agency to implement a comprehensive regulatory scheme in a technical area, it is appropriate to give weight to the agency's conclusion that state regulation would pose an obstacle to the achievement of federal objectives: "The agency is likely to have a thorough understanding of its own regulation and its objectives and is uniquely qualified to comprehend the likely impact of state requirements." 529 U.S. at 883 (internal quotation marks omitted); *see also Lohr*, 518 U.S. at 496 ("Because the FDA is the federal agency to which Congress has delegated its authority to implement the provisions of the Act, the agency is uniquely qualified to determine whether a particular form of state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." (footnote and internal quotation marks omitted)); *Colacicco* v. *Apotex, Inc.*, 521 F.3d 253, 274-276 (3d Cir. 2008) (FDA's view that imposition of liability under state law for failure to warn would interfere with federal regulatory objectives is entitled to deference).

achievement of Congress's objectives, the claims are preempted.[23]

C. The 1962 Amendments To The FDCA Do Not Limit The Application Of This Court's Settled Conflict Preemption Principles

The Vermont Supreme Court rejected Wyeth's argument that respondent's state-law claims present an obstacle to Congress's purposes and objectives on the ground that section 202 of the 1962 Amendments to the FDCA limited the statute's preemptive effect to cases where compliance with both state and federal law was impossible. Pet. App. 21a. Section 202 states:

> Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law . . . unless there is a direct and positive conflict between such amendments and such provision of State law.

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[23] No "presumption against preemption" applies to alter this analysis. Regulation of drug labeling has now been the domain of the federal government for more than a century, and there is no presumption against federal preemption when States regulate in an area where there has been a history of significant federal presence. *United States* v. *Locke*, 529 U.S. 89, 108 (2000); *see also Buckman*, 531 U.S. at 347-348. Even where the presumption does apply, the existence of an actual conflict between federal and state law, even if implied, requires the state law to yield notwithstanding the presumption. *See Felder* v. *Casey*, 487 U.S. 131, 138 (1988) ("'[A]ny state law, however clearly within a State's acknowledged power, which interferes with or is contrary to federal law, must yield.'" (quoting *Free* v. *Bland*, 369 U.S. 663, 666 (1962)); *de la Cuesta*, 458 U.S. at 153 ("The relative importance to the State of its own law is not material when there is a conflict with a valid federal law, for the Framers of our Constitution provided that the federal law must prevail." (internal quotation marks omitted)).

Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962). In the Vermont Supreme Court's view, a "direct and positive conflict" exists only where compliance with both federal and state law is a physical impossibility. Pet. App. 21a-22a. Its rejection of Wyeth's "impossibility" argument was therefore "a complete answer to the question of preemption." Pet. App. 23a. That conclusion was incorrect.

It is far from clear whether section 202 addresses the preemptive scope of any part of the FDCA regime other than "the amendments made by" the 1962 Act. *See* U.S. Br. 16. But even if section 202 is relevant here, it would not preclude preemption in this case, because that section does nothing more than make clear that the FDCA does not occupy the entire field of all matters relating to prescription drugs, a claim that is not implicated here. By using the phrase "direct and positive conflict," Congress endorsed application of conflict preemption principles, using language from this Court's decisions with a well-settled meaning that includes both "impossibility" and "obstacle" conflict preemption. *See, e.g.*, *Sinnot* v. *Davenport*, 63 U.S. (22 How.) 227, 242-243 (1859) (finding "direct and positive" conflict between federal and state licensing provisions despite possibility of dual compliance); *Missouri, Kan. & Tex. Ry. Co.* v. *Haber*, 169 U.S. 613, 623 (1898) (test for "direct and positive conflict" is whether state provisions may "stand without obstructing or embarrassing the execution of the act of Congress"); *see also Phillips* v. *General Fin. Corp. of Fla.*, 297 So. 2d 6, 8 (Fla. 1974) (test for "direct and positive conflict" is "whether the state law frustrates the operation of the federal law and prevents the accomplishment of its purpose"); *Oefinger* v. *Zimmerman*, 601 F. Supp. 405, 412-413 (W.D. Pa. 1984) (analyzing whether "direct and positive conflict"

existed between state law and federal law under principle of "obstacle" conflict preemption), *aff'd*, 779 F.2d 43 (3d Cir. 1985); *Conkle* v. *Wolfe*, 722 N.E.2d 586, 593-594 (Ohio Ct. App. 1998) (same). Indeed, as this Court has explained:

> The Court has not previously driven a legal wedge—only a terminological one—between "conflicts" that prevent or frustrate the accomplishment of a federal objective and "conflicts" that make it "impossible" for private parties to comply with both state and federal law. Rather, it has said that both forms of conflicting state law are "nullified" by the Supremacy Clause, and it has assumed that Congress would not want either kind of conflict.

Geier, 529 U.S. at 873 (citations omitted). The Third Circuit recently confirmed this view, holding that the "direct and positive conflict" provision in section 202 "merely states that conflict preemption applies." *Colacicco* v. *Apotex Inc.*, 521 F.3d 253, 262 n.8 (3d Cir. 2008).

Consistent with this case law, Congress used the term "direct and positive conflict" in the 1962 Amendments not to narrow conflict preemption, but to foreclose claims of "field preemption"—which is not at issue here—and avoid the ouster of non-conflicting state-law requirements based on the comprehensiveness of FDA's authority under the 1962 Amendments. As a sponsor of the Amendments explained:

> [T]here are some confusing decisions of the Court which hold that whenever the Congress enacts a law it preempts jurisdiction over all matter contained in the act to the exclusion of all State laws. . . . This would merely say that

> this Food and Drug Act shall not be construed as the intent of Congress to abolish all State laws on the same subject where they are not in conflict with the Federal law.

108 Cong. Rec. 21,083 (1962) (statement of Rep. Smith). That was consistent with a then-recent Supreme Court decision that used the phrase "direct and positive" to distinguish conflict preemption from field preemption. *See United Constr. Workers* v. *Laburnum Constr. Corp.*, 347 U.S. 656, 663 & n.5 (1954).[24]

In sum, section 202 does not support the implausible conclusion that Congress would tolerate an actual conflict between state and federal law that defeats the purposes of its own legislation and upsets the carefully crafted balance Congress and FDA have reached between the competing objectives of maximizing safety and maximizing therapeutic benefit. Such a conflict exists here. Respondent's claims are therefore preempted.

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[24] The Vermont Supreme Court relied solely on the Fourth Circuit's decision in *Southern Blasting Services, Inc.* v. *Wilkes County, North Carolina*, 288 F.3d 584 (4th Cir. 2002). But that decision merely held that a preemption clause requiring "direct and positive conflict" signified only that "Congress did not intend to occupy the field" and "simply restates the principle that state law is superseded in cases of an actual conflict with federal law." *Id.* at 590-591. Although the court recited only the "impossibility" prong of the conflict preemption standard, *id.* at 591, it in fact went on to consider whether the local ordinances at issue could be reconciled with congressional purposes and objectives—the essence of an "obstacle" conflict preemption analysis. *Id.* at 592.

CONCLUSION

The judgment of the Vermont Supreme Court should be reversed.

Respectfully submitted.

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